UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/167,088	10/06/1998	FRED D. FINKELMAN	91830/625	9944

26874 7590 03/11/2003

FROST BROWN TODD, LLC
2200 PNC CENTER
201 E. FIFTH STREET
CINCINNATI, OH 45202

EXAMINER	
GABEL, GAILENE 22	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/167,088	Applicant(s) FINKELMAN ET AL.	
	Examiner Gailene R. Gabel	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-23 and 25-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-23 and 25-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 1/6/03 in Paper No. 21 is acknowledged and has been entered. Claims 1, 4, 7, 13-15, 20, 25, 26, 31, 34, and 37 have been amended. Accordingly, claims 1, 4-23 and 25-42 are pending and under examination.

It is noted that the pages and lines that are made reference to in page 5, paragraph 1 of Applicant's response do not fully correlate with the instant specification. All pages in the specification include lines 1-23 per page and do not seem to include lines 24-29 as referred to by Applicant.

Rejections Withdrawn

Claim Rejections - 35 USC § 112/103

2. In light of Applicant's amendment and arguments, the rejection of claims 1, 4-23 and 25-42 under 35 U.S.C. 103(a) as being unpatentable over Tamarkin et al. (US 5,587,294) in view of Pouletty et al. (US 5,612,034) is hereby, withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 4-23, and 25-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step i) is vague and indefinite in reciting, "wherein the target analyte is ... peptide or protein hormone or cytokine" because it appears that the method is drawn to measuring the production of secreted analyte as required by the preamble. Perhaps Applicant intends that the target analyte is "secreted peptide" or "secreted protein hormone". Alternatively, it is unclear how cytokine which is typically an intracellular protein is measured using the claimed method.

Claim 20 is indefinite in reciting, "wherein the second targeting moiety binds specifically to the first targeting moiety, wherein the second targeting moiety is injected in sufficient quantity that a measurable fraction of first targeting is bound by the second targeting moiety" because it is unclear what structural and functional cooperative relationship exists between the second targeting moiety and the desired target analyte. Specifically, does the second targeting moiety bind the first targeting moiety regardless of whether the first targeting moiety is bound to a target analyte. Accordingly, it is unclear how the second targeting moiety plays a role in the detection or measurement of the production of secreted target analyte.

Claim 25 remains confusing in reciting, "the means for detecting the ... complexes" because the term "means" implies an element or an apparatus rather than as assay. Perhaps Applicant intends "wherein the targeting moiety:target analyte:capture moiety complexes are detected by radioimmunoassay."

Claim 31 remains confusing in reciting, "capture moiety is labeled by linking to a fluorescent labeling compound". It may be clarified by the following language, "capture moiety is labeled with a fluorescent label".

Claim 34 remains confusing in reciting, "the label is an enzyme indicating means operatively linked to the targeting moiety" because the term "means" implies an element or an apparatus accompanying the enzyme. Perhaps Applicant intends "the label is an enzyme that is operatively linked to the targeting moiety."

Claim 34 is vague and indefinite in reciting, "the second reagent comprises a capture moiety specific for the target analyte even when such target analyte is conjugated with the labeled targeting moiety" because it appears that in order to be useful in detecting the presence of target analyte as recited in claim 1, the capture analyte is required to capture the target analyte that is conjugated with the labeled targeting moiety; thus forming the "targeting moiety:target analyte:capture moiety complexes. See also claim 37.

Claim 37 remains indefinite, confusing, and inconsistent in relation to claim 20 from which it depends in reciting, "having first targeting moieties ... that immunoreact with a target analyte ...and having second targeting moieties that immunoreact with the target analyte at a site different from the first targeting moieties" because claim 20 recites that "the second targeting moiety binds specifically to the first targeting moiety and not the target analyte at a different site from the first targeting moieties". Please clarify the claims or otherwise correct.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 4-23 and 25-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In this case, the specification does not appear to provide literal or descriptive support for the recitation of "the targeting moiety is injected in sufficient quantity that a measurable fraction of target analyte is bound by the labeled neutralizing targeting moiety" in claim 1. Applicant points to page 16, lines 19-24 for support wherein the specification provides that the targeting moiety is injected and allowed to circulate throughout the body and page 18, lines 13-16 wherein it is stated that the targeting moiety causes the cytokine which has short in vivo half-life to accumulate in vivo as a complexes; however, there is no literal or descriptive support to encompass the recitation of "a sufficient quantity (so as to obtain) a measurable fraction of target analyte [that is] bound by the labeled neutralizing targeting moiety." The specification further does not appear to provide literal or descriptive support for the recitation of "obtaining a sample ... after a defined period of time" which is "from about 1 hour to 72 hours" in claims 1 and 14, respectively. Applicant points to page 15, lines 3-10 for support but fails to provide literal or descriptive support for this limitation in question.

Limitations in claims that lack literal or descriptive support in the specification constitute new matter.

5. Claims 1, 4-23 and 25-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for in vivo targeting, in vitro capturing, and measuring production of secreted cytokines, secreted peptides and protein hormones in the blood, does not reasonably provide enablement for in vivo targeting, in vitro capturing, and measuring of any other peptide, protein, or cytokine, i.e. intracellular, in the peripheral blood. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method for measuring in vivo production of secreted cytokine, secreted peptide, or secreted protein hormone as target analyte of interest in a human or animal by injecting a neutralizing targeting

moiety to the human or animal to allow binding of the targeting moiety to secreted cytokine or secreted peptides and protein hormones; thus forming complexes therebetween in vivo, and then reacting the complexes in vitro with a capture moiety for detecting and measuring the amount of secreted peptides or secreted protein complexes in an assay detection method.

The state of the prior art- the prior art of record fails to disclose a method wherein the targeting moiety is injected to bind any and all cytokines, i.e. intracellular, peptides or protein hormones in vivo then reacted with a capture moiety in vitro, to detect the presence or amount of targeting moiety - target analyte complexes.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed method will work in any and all cytokines, peptides or protein hormones that occur in vivo in human and animals.

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed method to work for measuring production of secreted cytokines or secreted peptides and proteins in a human or animal. However, the specification fails to provide guidance to enable the claimed method to work for any and all cytokines, i.e. intracellular, peptides or protein hormones in human and animals.

The presence or absence of working examples- working examples are provided in the specification that show that the claimed method works for measuring production of secreted cytokines in a human or animal. There are no working examples that show analogous results in any other cytokine, i.e. intracellular, peptide or protein hormone in vivo which is encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed for measuring the production of any cytokine, peptide, or protein that is not secreted in circulation, i.e. intracellular cytokine or protein.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method for measuring in vivo production of cytokine, peptide, or protein hormone as target analyte of interest in a human or animal by injecting a neutralizing targeting moiety to the human or animal to allow binding of the targeting moiety to the cytokine or peptide or protein hormone; thus forming complexes therebetween in vivo, and then reacting the complexes in vitro with a capture moiety for detecting and measuring the amount of peptide or protein complexes in an assay detection method.

While the specification at page 18, lines 8-20 and page 20-23 describes using anti-cytokine antibody (or cytokine binding molecules) as neutralizing targeting moiety for injection into human or animal to bind secreted cytokine in vivo, thus, causing accumulation of in vivo cytokine-anti-cytokine antibody complexes, and then binding the complexes to polyclonal capture antibodies immobilized into solid phase for assay detection in vitro, nowhere in the specification describes any other neutralizing targeting moiety that binds any other non-secreted and non-circulating cytokine or peptide or protein hormone to cause accumulation of such complexes in vivo, then reacts the complexes with capture antibodies in vitro, for use in a detection method of the cytokine or peptide or protein hormone. The specification does not establish a direct correlation

between secreted cytokines and other secreted peptides or protein hormones, which would lead the skilled artisan to say that if the claimed method works for measuring endogenous secreted cytokine production, then it should work in all other intracellular or endogenous peptides and protein hormones in a human or animal, to enable the breadth of the claimed method. Further, all working examples exemplify measuring in vivo production of endogenous secreted cytokine using the claimed method. Additionally, in page 12, lines 20-25 of the specification, Applicant defines that the antibody for use as a neutralizing targeting moiety is "prototypical". While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed method is enabled. This is not the case in the instant specification. Thus, the claimed method is only enabled for measuring in vivo production of secreted cytokines, secreted peptides and protein hormones as the target analyte.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable detection of in vivo production of any and all peptides and protein hormones using the claimed invention, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work in any and all cytokines, i.e. intracellular, peptides or protein hormones; 3) there is no proper guidance that shows that the method can be performed for measuring the amount of any and all endogenous

peptides and protein hormones in the instant specification, 4) the nature of the invention is a method for measuring in vivo production of secreted cytokines, secreted peptides, or secreted protein hormones as target analyte of interest in a human or animal by injecting a neutralizing targeting moiety to the human or animal to allow in vivo binding of the targeting moiety to the secreted cytokine, secreted peptide or secreted protein hormone; thus forming complexes therebetween and then reacting the complexes with a capture moiety in vitro for assay, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that prior art of record fails to disclose a method applicable for measuring an amount of any and all endogenous peptides or protein hormones in a human or animal, and lastly 7) the claims broadly recite a method for measuring in vivo production of cytokines, i.e. intracellular, peptides or protein hormones as target analyte of interest in a human or animal by injecting a neutralizing targeting moiety to the human or animal to allow binding of the targeting moiety to the peptide or protein hormone; thus forming complexes therebetween in vivo, and then reacting the complexes in vitro with a capture moiety for detecting and measuring the amount of peptide or protein complexes in an assay detection method. As recited, the instant method will measure in vivo production of any and all peptides or protein hormones, regardless of where or how they are produced.

Therefore, it is maintained that one of skill in the art could not make and use the invention as claimed without undue experimentation.

Response to Arguments

6. Applicant's arguments, see pages 8-12, filed 12/23/02, with respect to the rejection of claims 1, 4-23, and 25-42 under 35 USC 112, first paragraph, enablement rejection, have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground of rejection is made in view of the amendment made to independent claim 1, step i), "wherein the target analyte is a secreted cytokine, *peptide, protein hormone, or cytokine*. Thus, while claims 1, 4-23, and 25-42 are enabled for secreted cytokines which are functionalized peptides, secreted peptides, and secreted protein hormones, they are not enabled for any other cytokine, i.e. intracellular, or any other endogenous non-circulating peptide, or protein hormone.

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Friday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays at 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
Art Unit 1641

3/8/03

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641
3/9/03